FGF-23

GATHERING THE EVIDENCE

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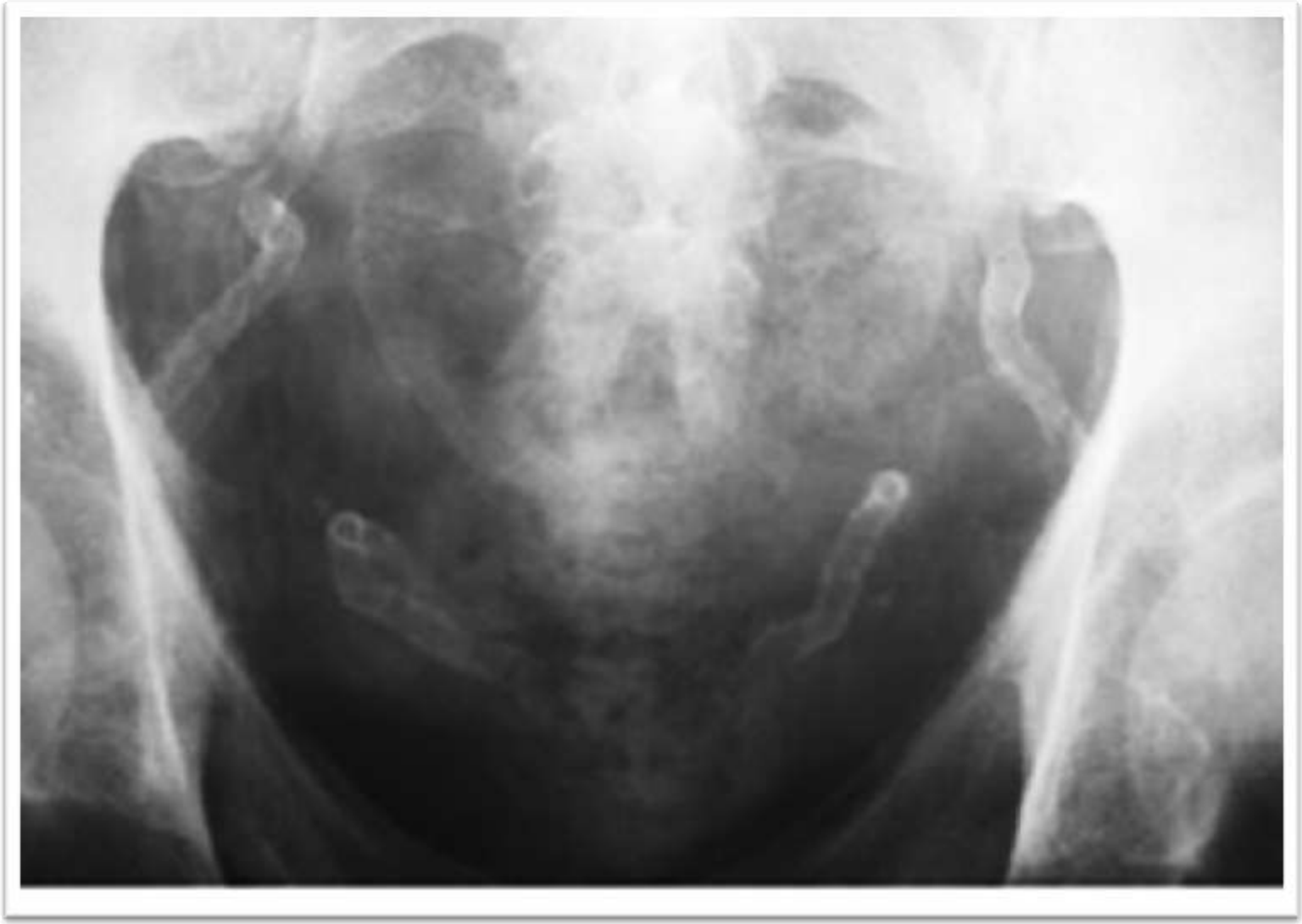
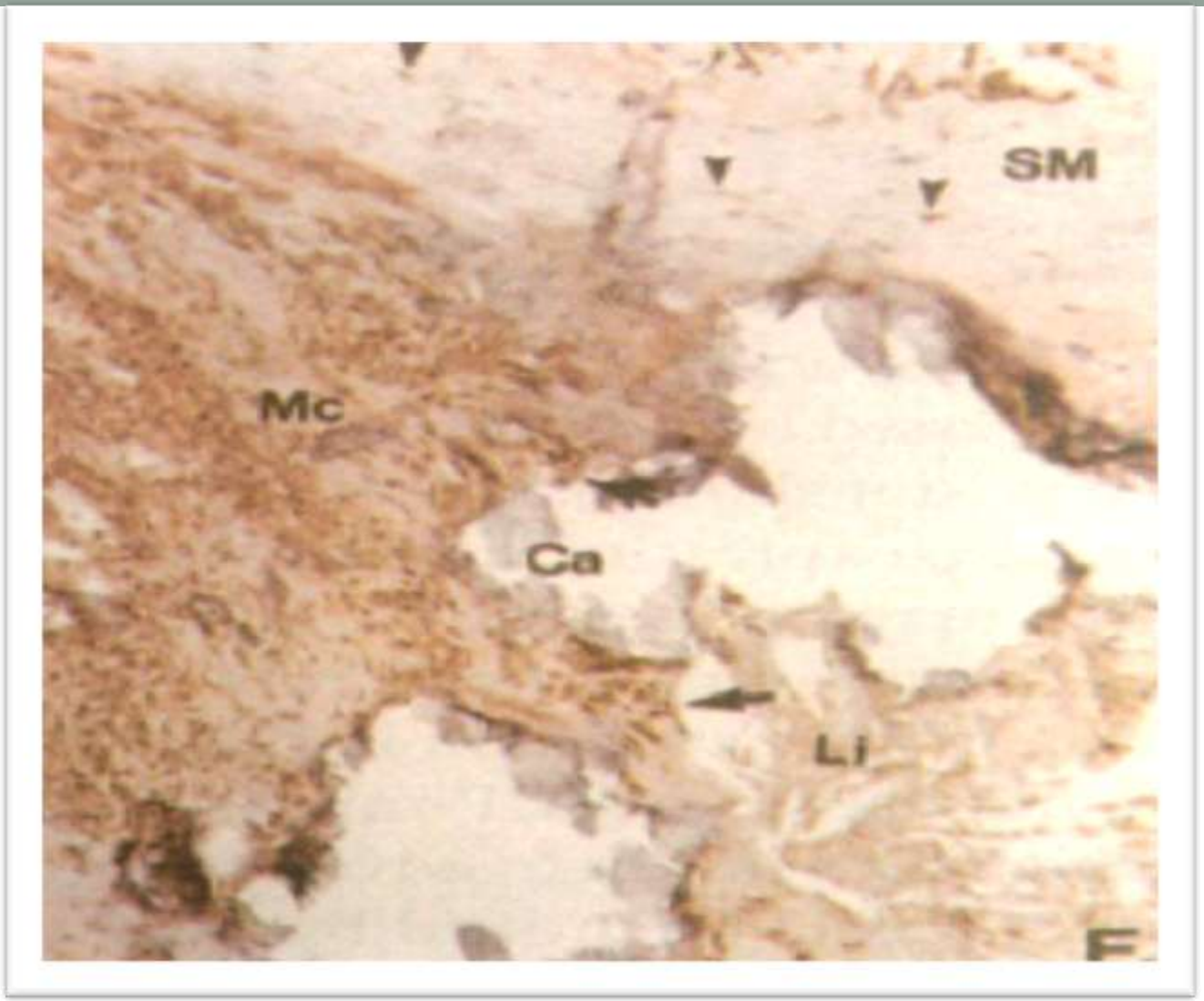
18-4-2014

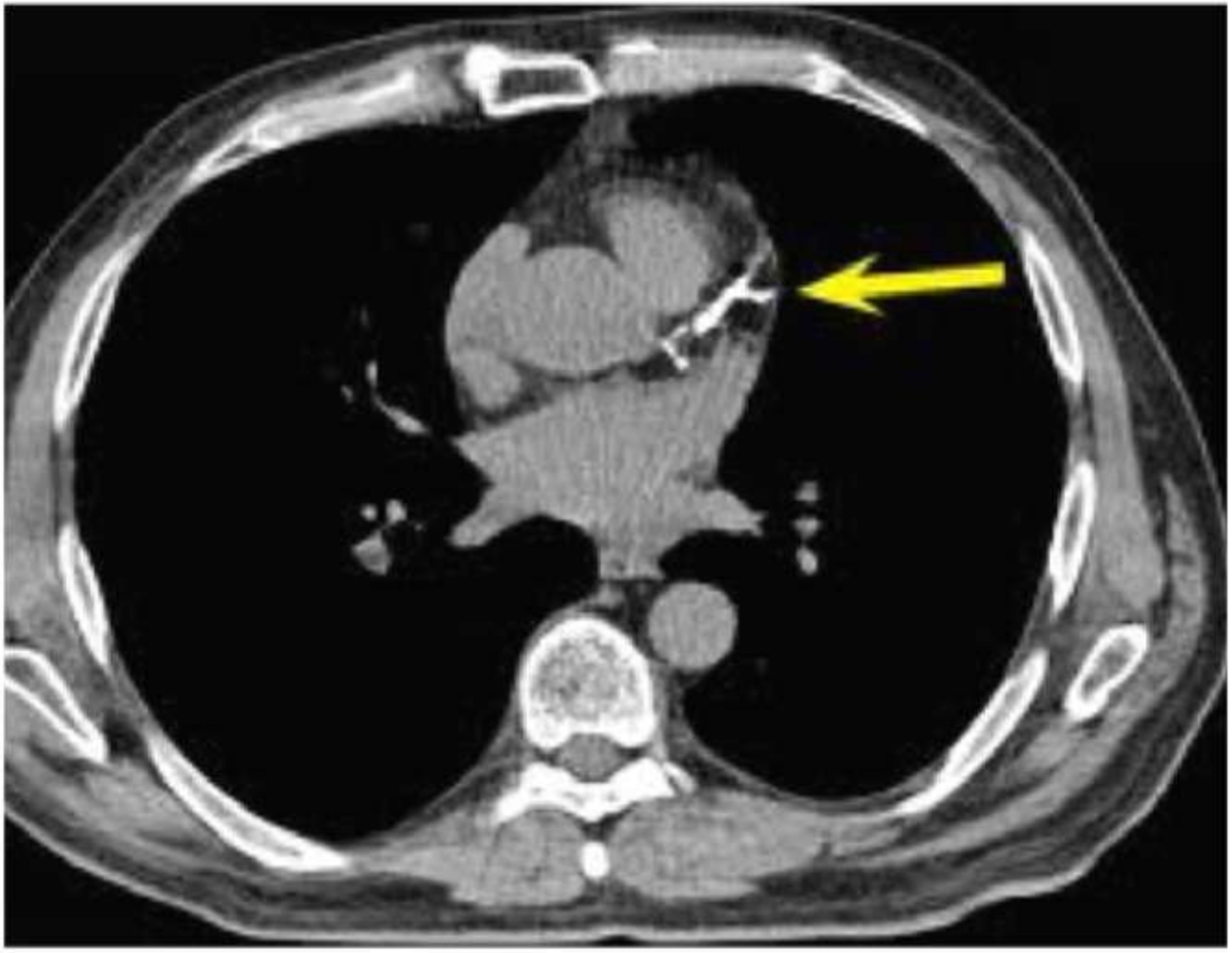


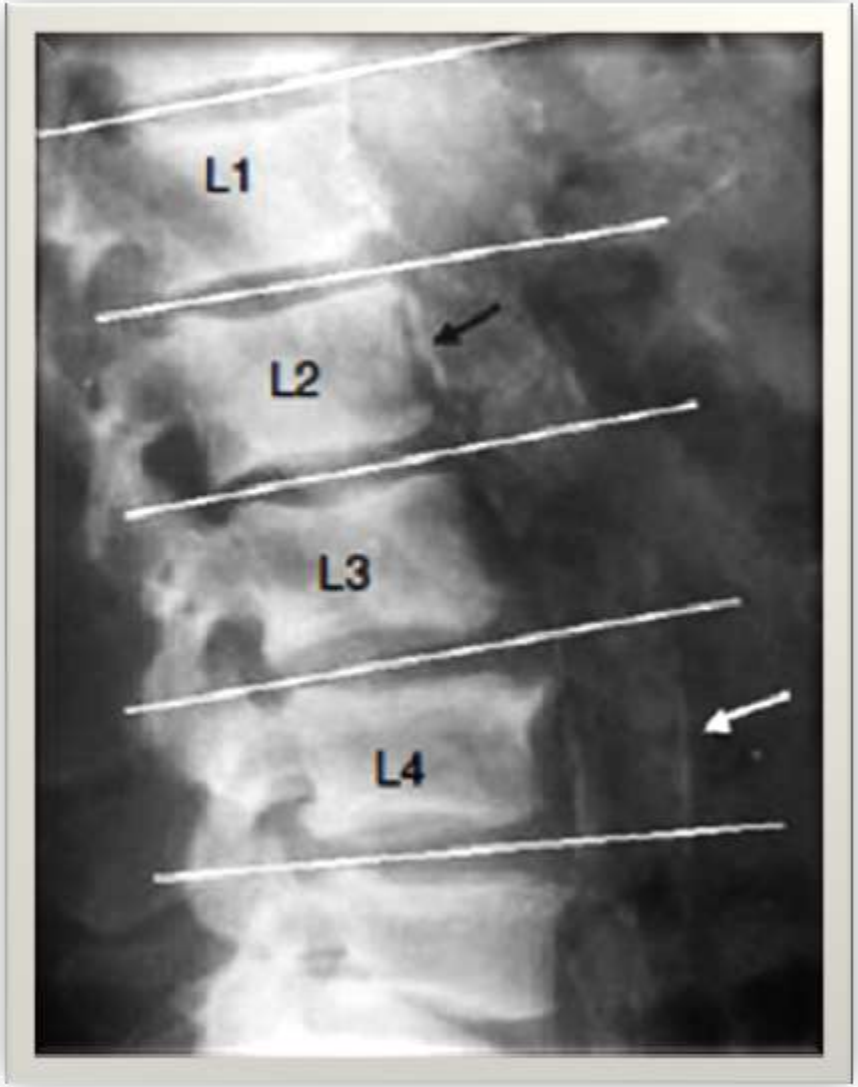
Adragao, 2003

FIRST THREAD



Shanahan et al, JCI, 1994




L1
L2
L3
L4

SECOND THREAD

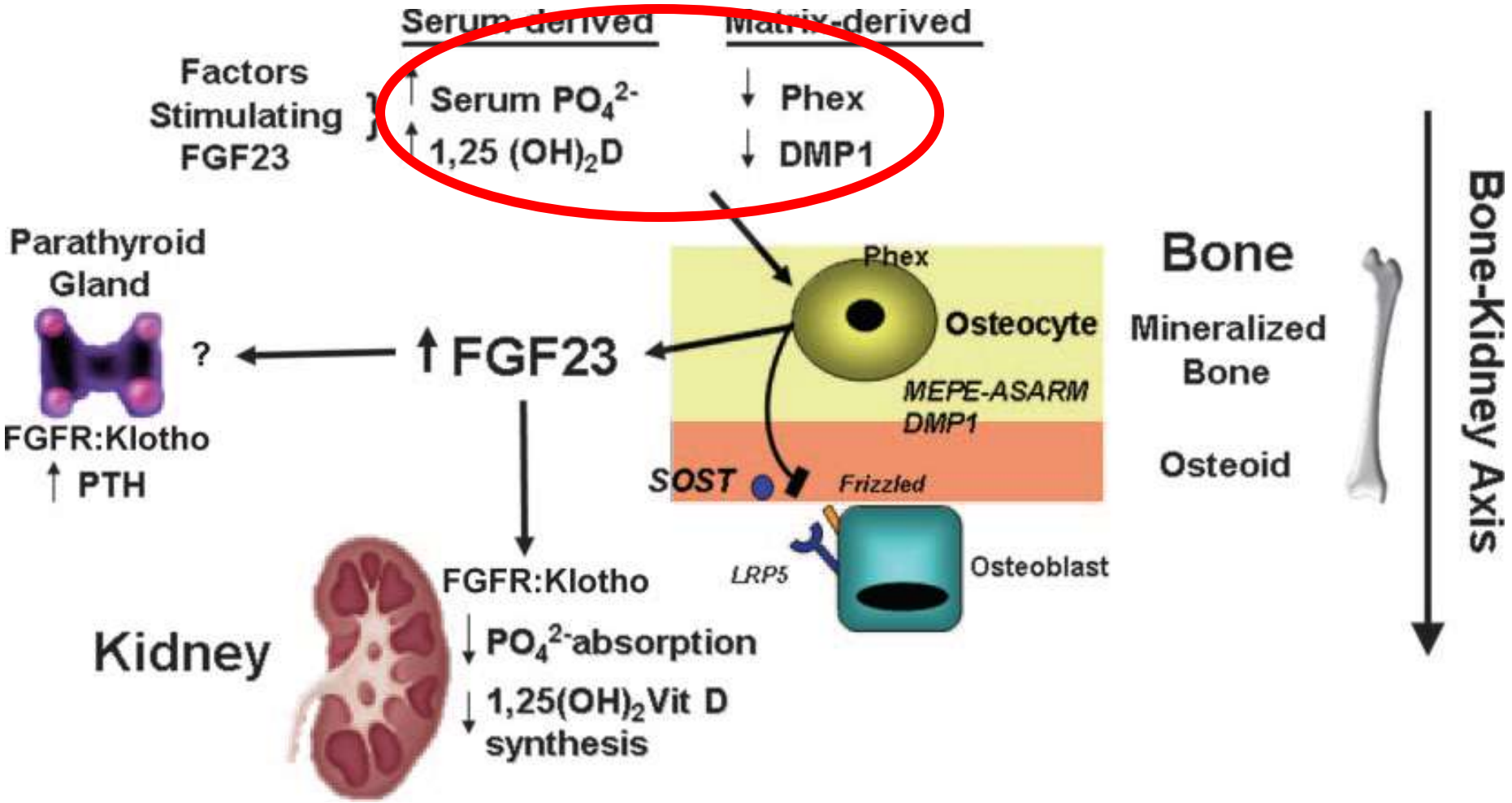
- X-linked
- AD
- AR
  - hypo-phosphatemic rickets

- Tumour induced osteomalacia

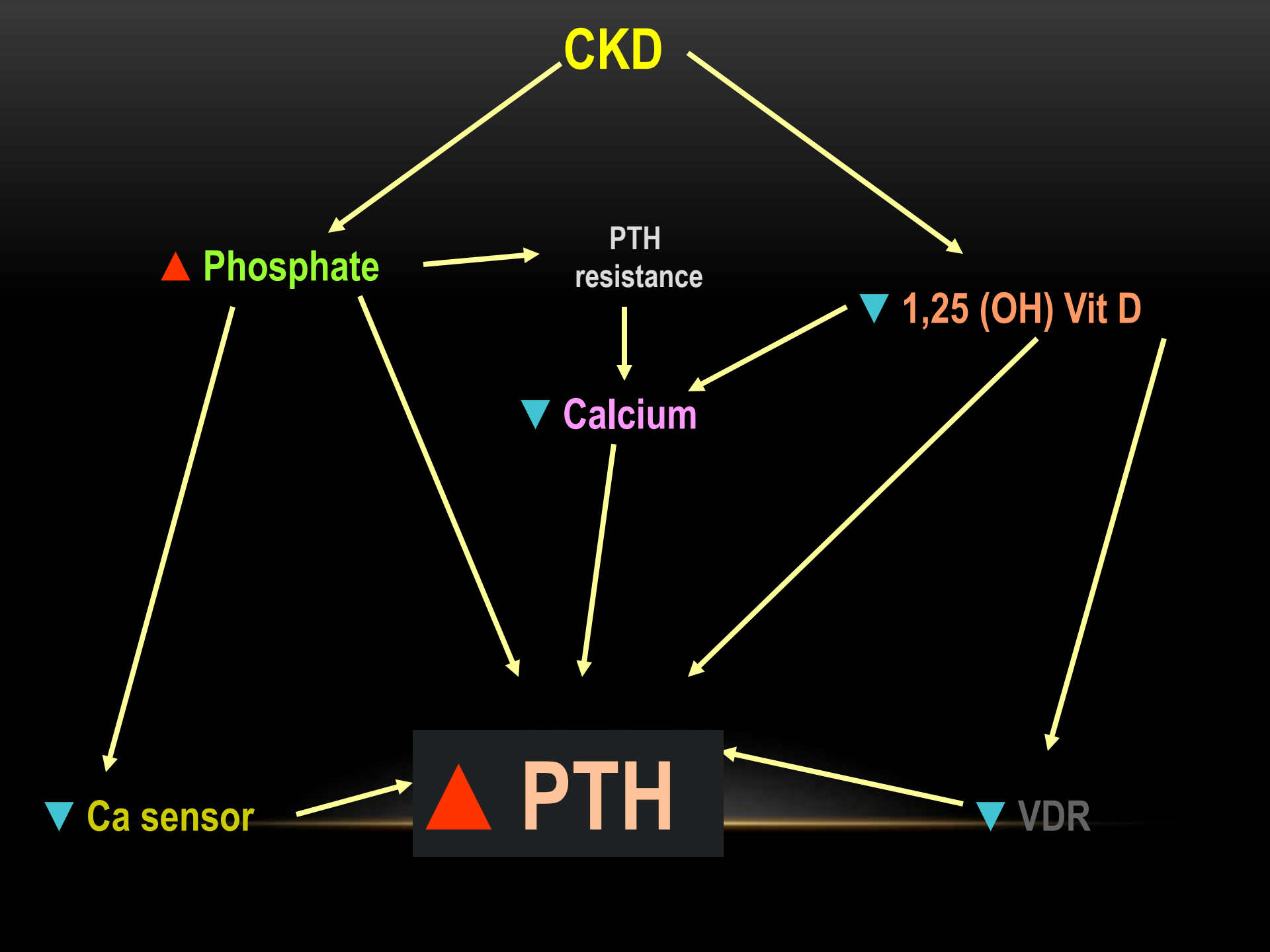
“Phospahatotonin”

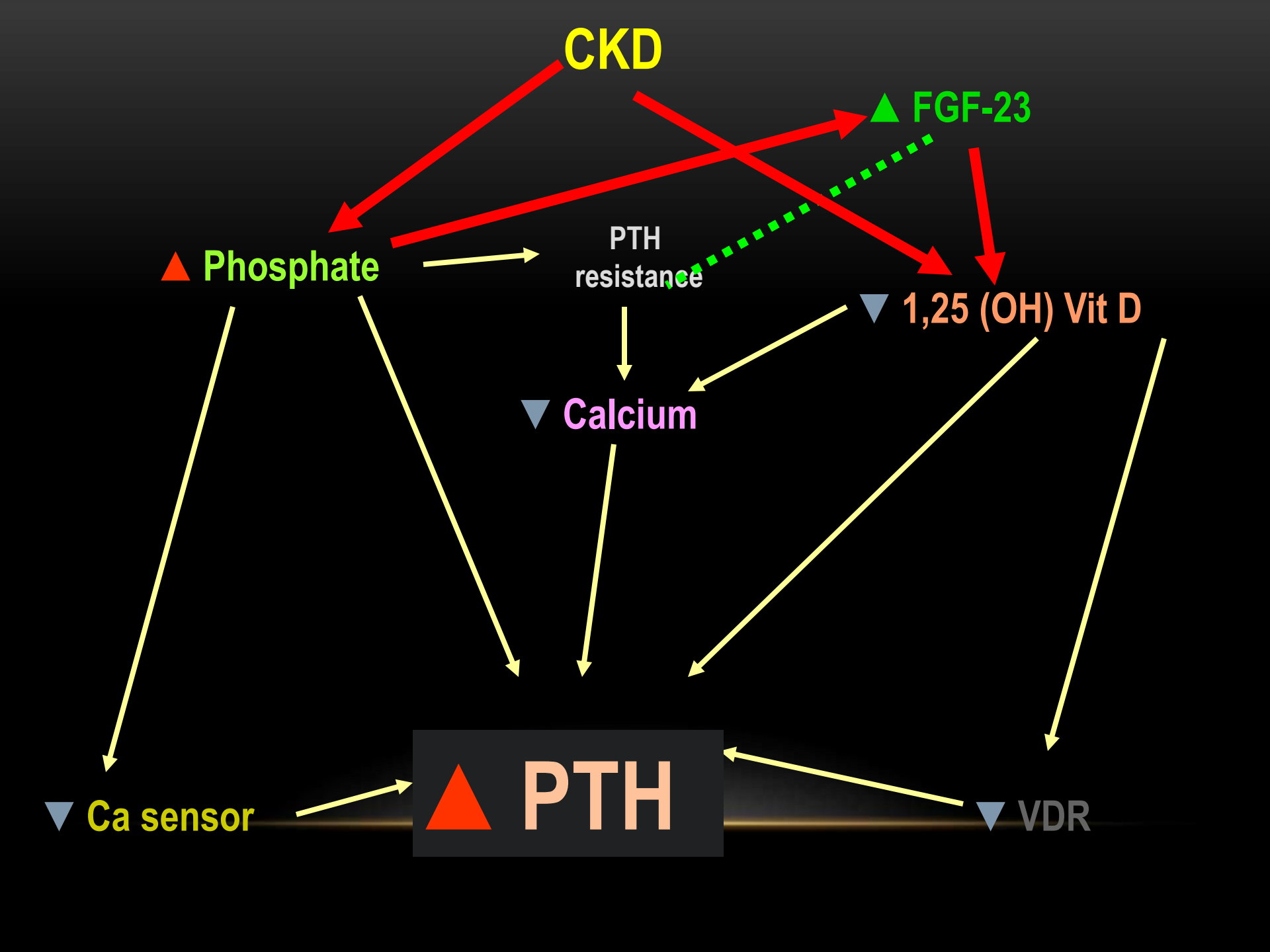
FGF-23, *the phosphatotonin*

- Identified in 2000
- DNA cloned from tumour tissue of patients with TIO, 2001
- Inhibits Na/Pi cotransporter IIa in the PCT
- Inhibits 1^{α} hydroxylation of vit D

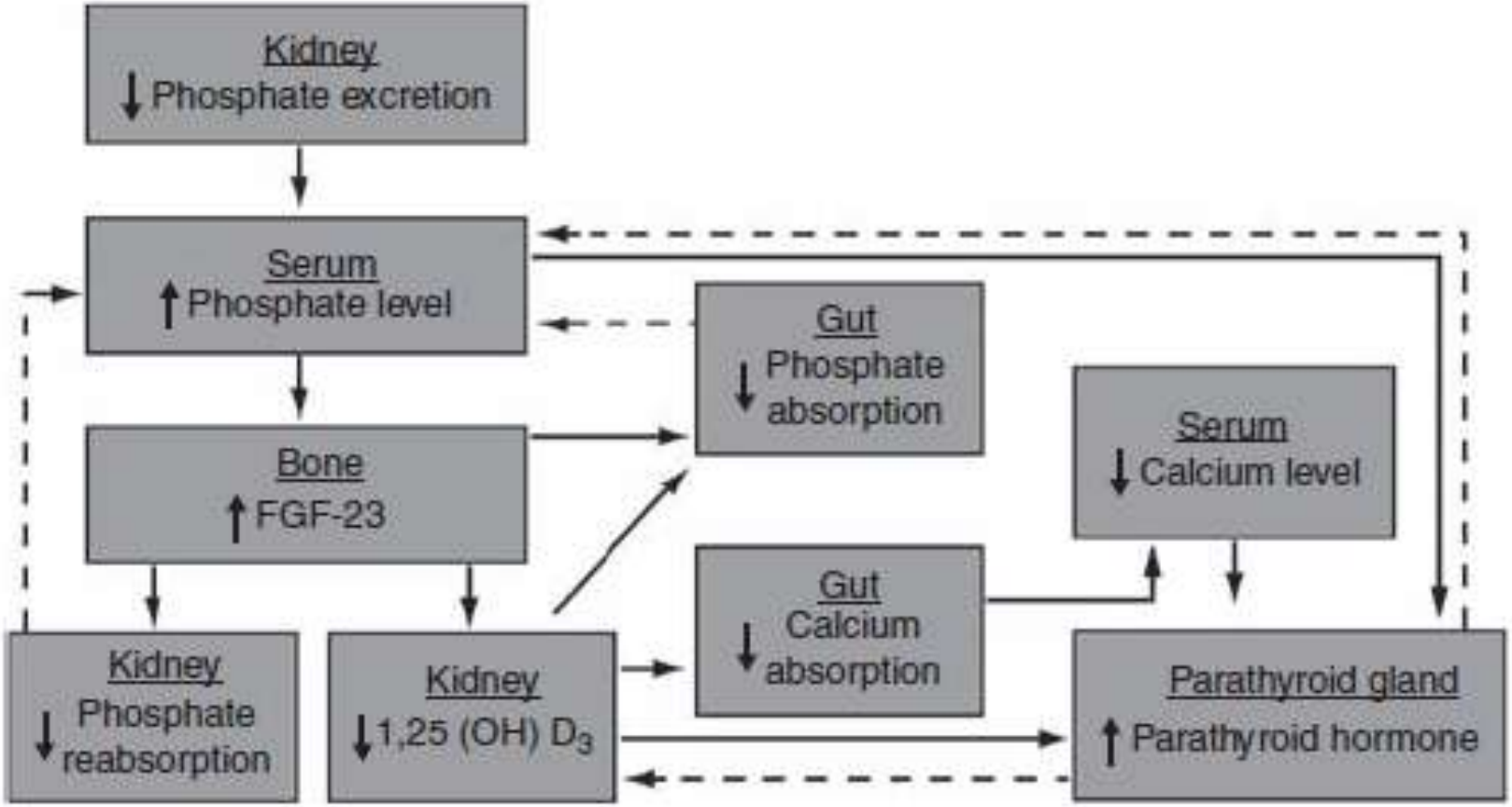


Liu and Quarles; JASN 2007


CKD
▲ Phosphate
PTH resistance
▼ 1,25 (OH) Vit D
▼ Calcium
▼ Ca sensor
▲ PTH
▼ VDR


CKD
▲ FGF-23
▲ Phosphate
PTH
resistance
▼ 1,25 (OH) Vit D
▼ Calcium
▼ Ca sensor
▲ PTH
▼ VDR

A new understanding of CKD-BMD

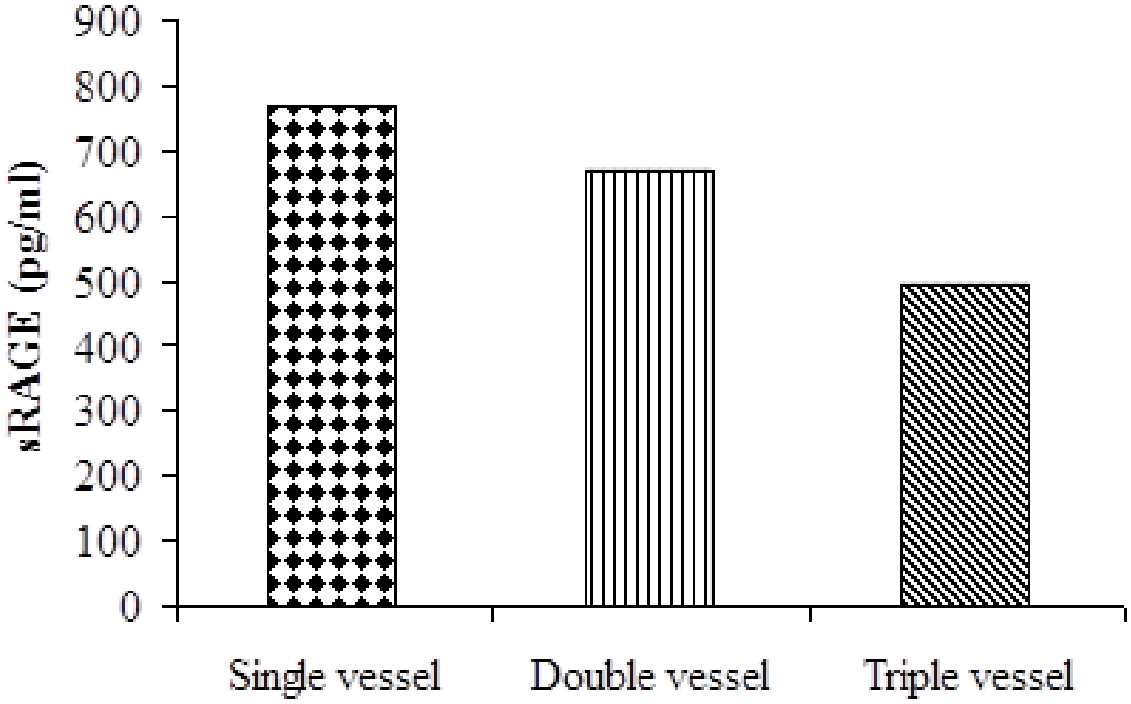


Seiler, KI, 2009

THIRD THREAD

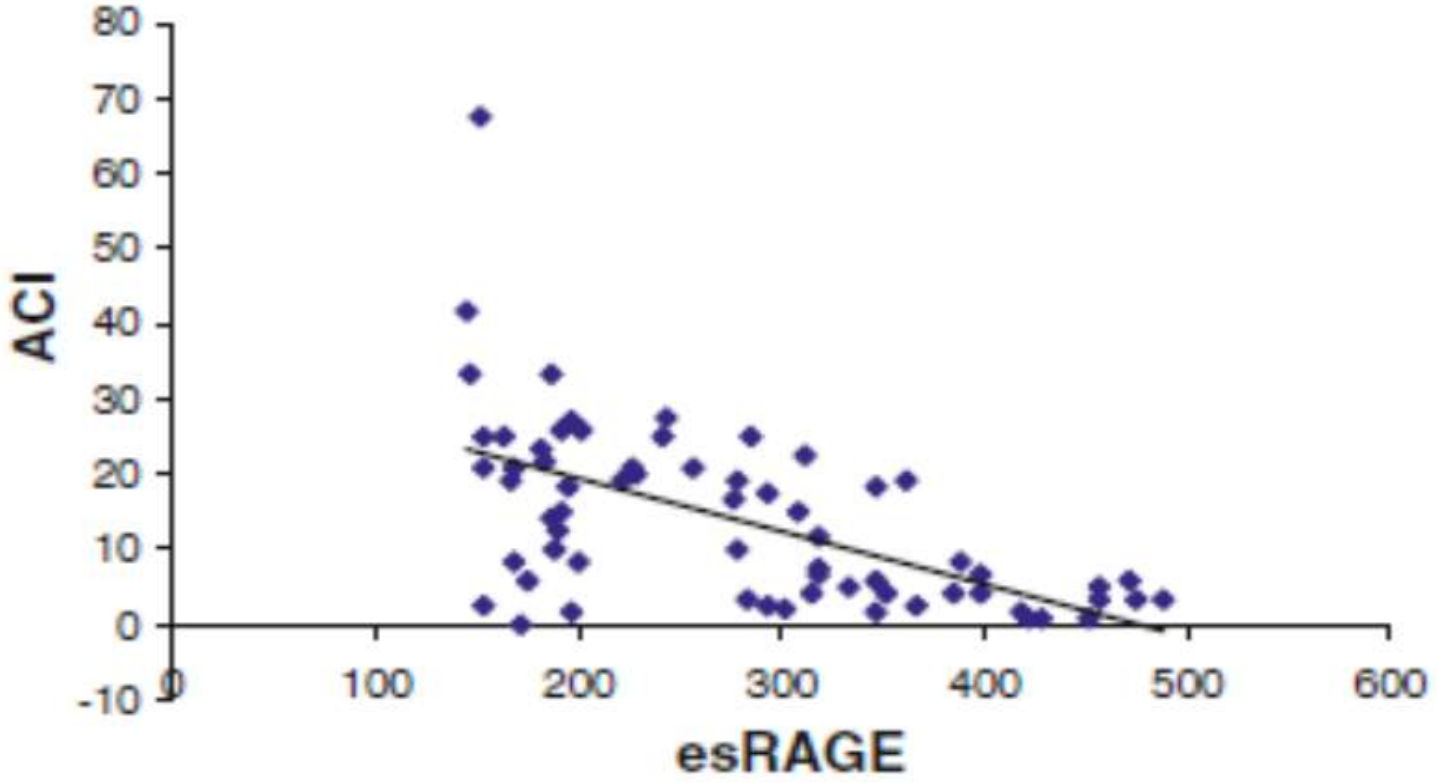
Inflammation

- Malnutrition-Inflammation-Atherosclerosis
  - CRP
  - R.O.S
  - AGE’s (in diabetics?)



Diab R et al, J Egy Soc Int Med 2007

esRAGE negatively associated with Aortic Calcification

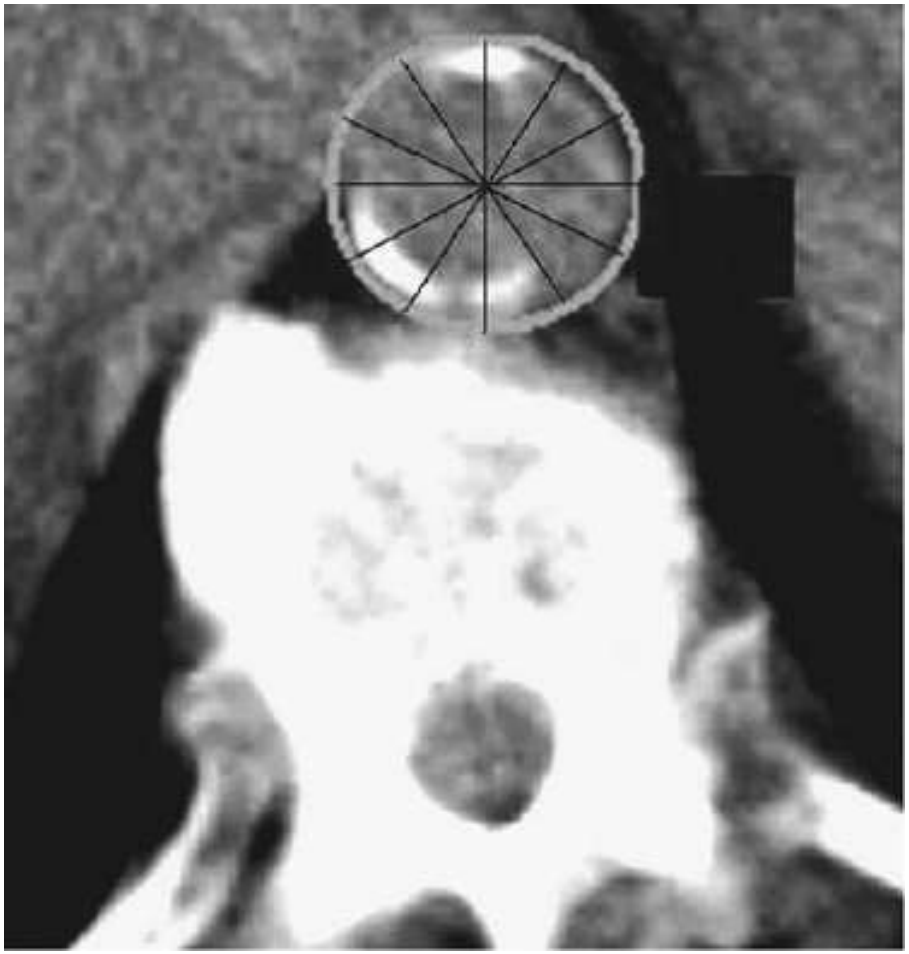


NasrAllah, 2012, Int Urol Nephrol

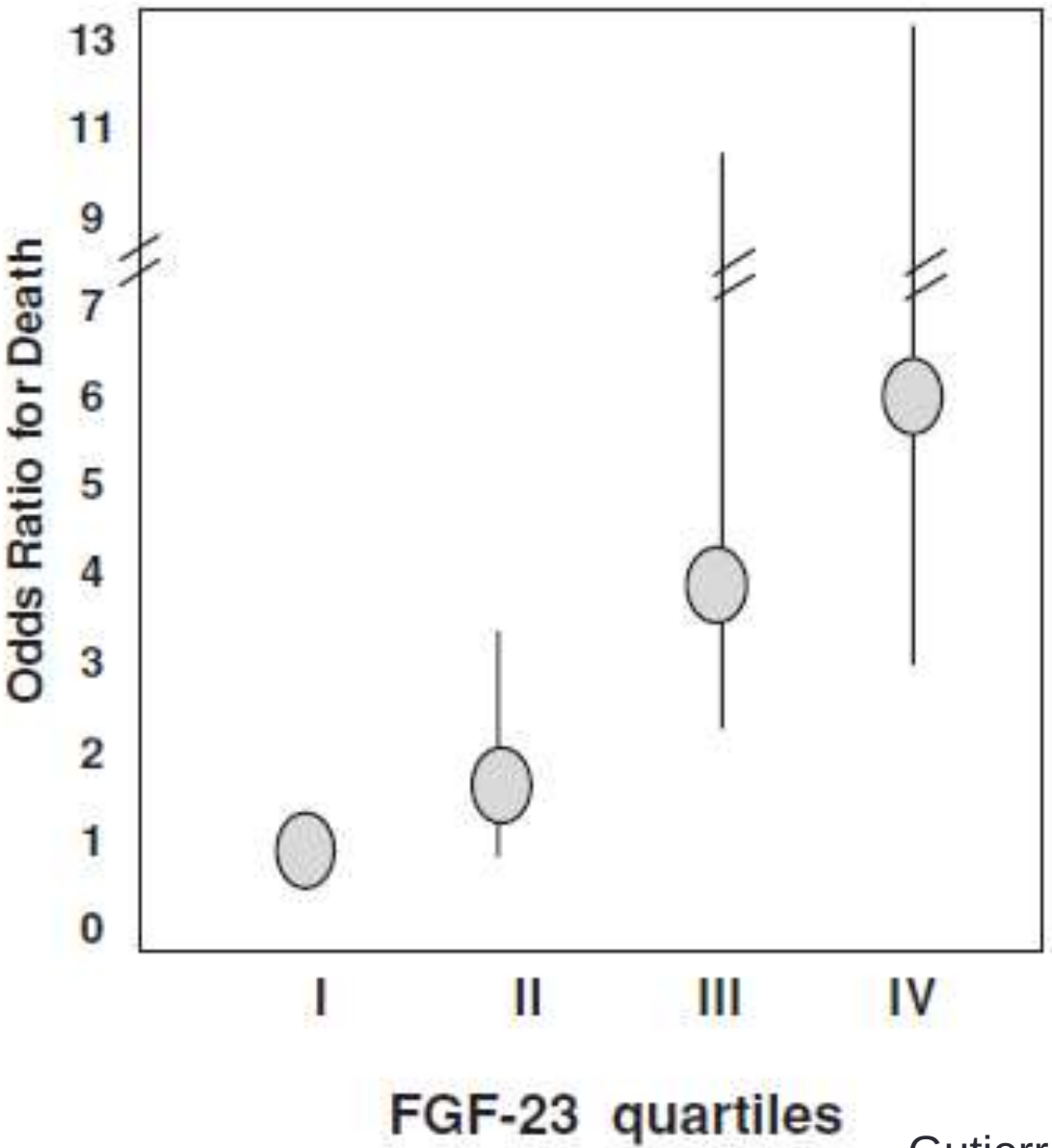
Putting it all together

- Hypothesis: FGF-23 protective against aortic calcification in CKD (??)

- Rationale:
  - Findings in animal models



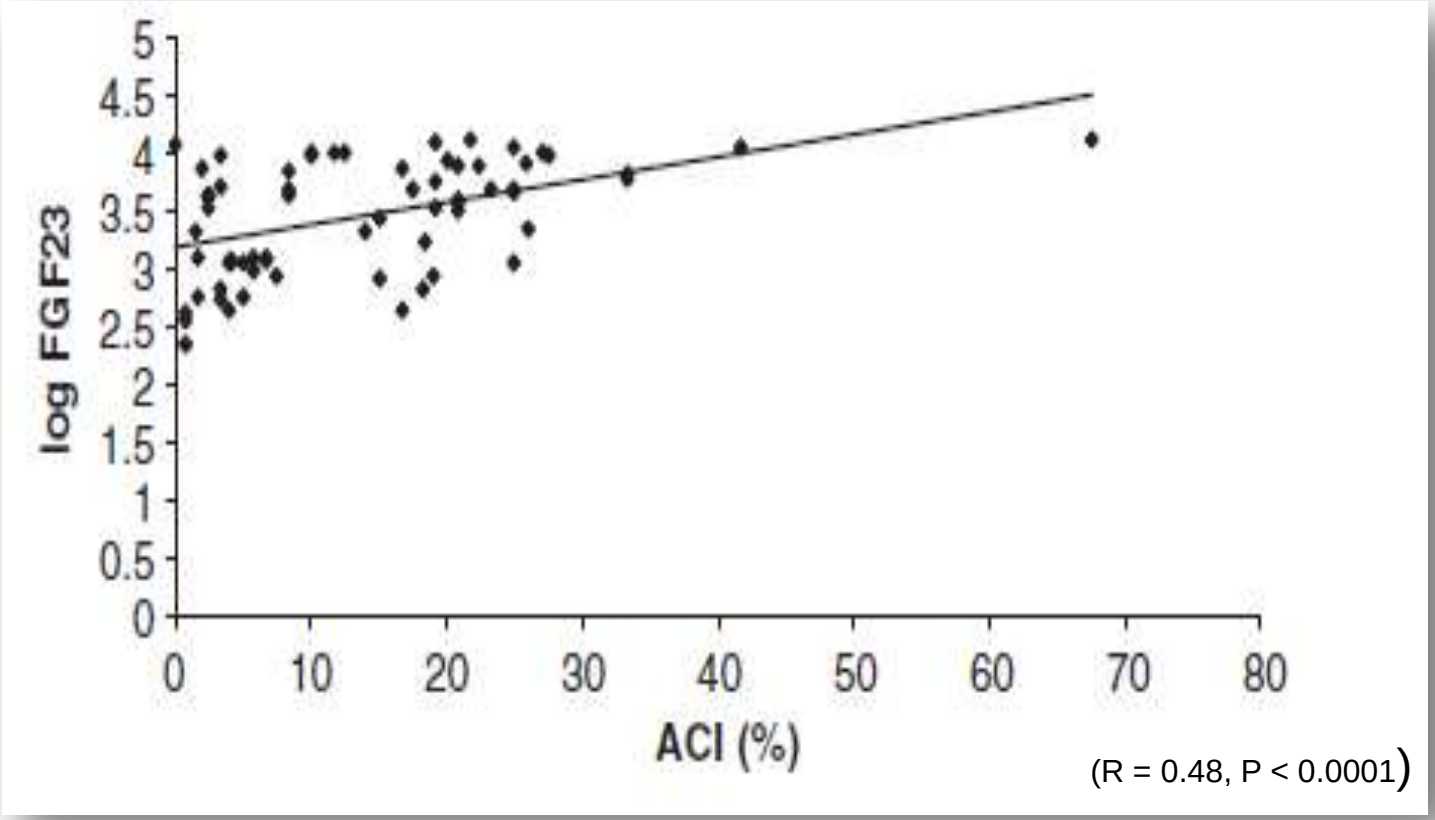
NasrAllah et al, NDT,2010



Gutierrez et al, NEJM 2008

FGF-23 40X that of controls

Aortic calcification was present in 98% (all but one) of our HDx patients

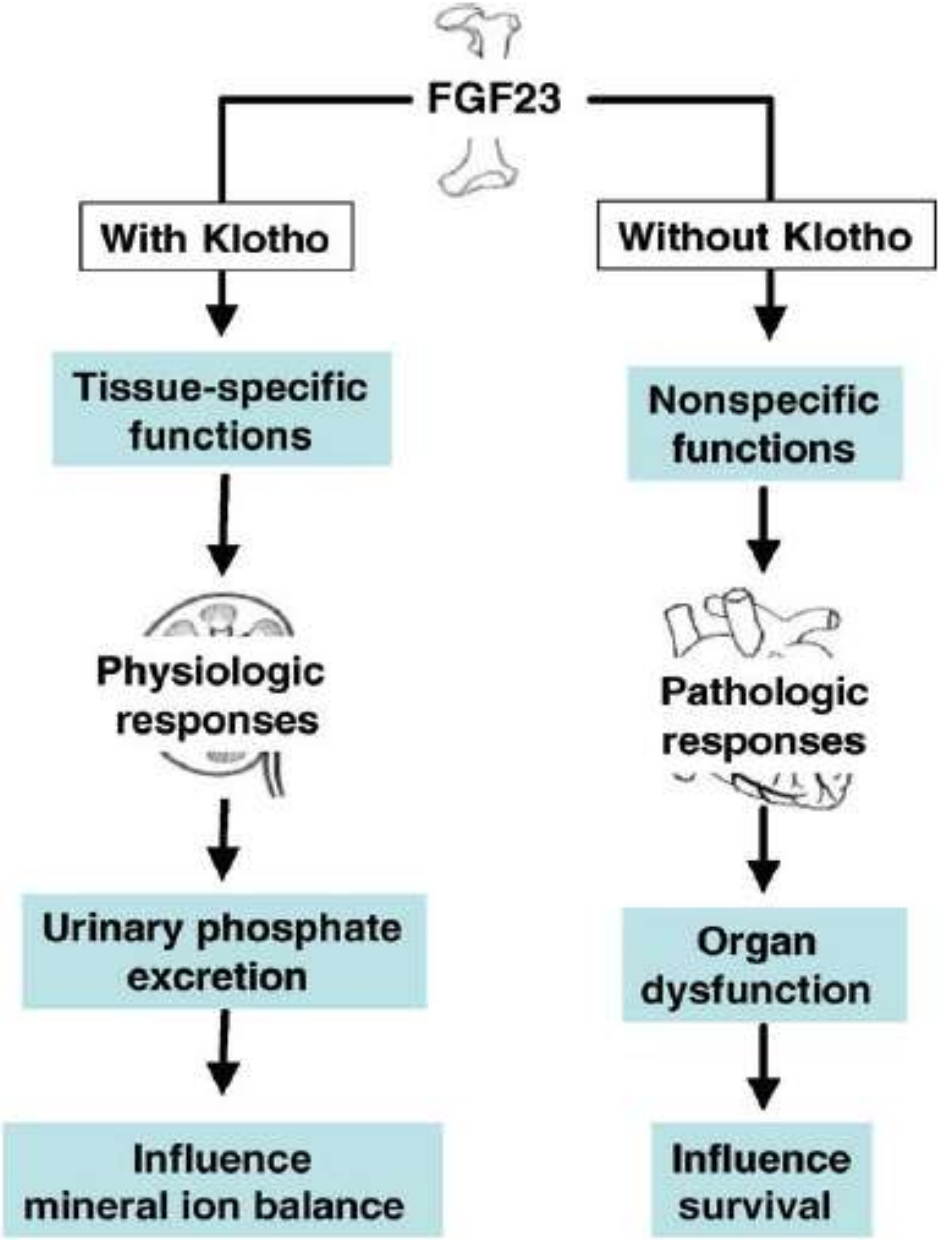


NasrAllah et al, NDT,2010

	Significance; *P*	β	95% CI
Pooled analysis: R^2 = 0.476			
FGF-23	<0.0001	0.58	0.001–0.002
Systolic BP	<0.0001	0.48	0.18–0.4
Incident: R^2 = 0.37			
FGF-23	0.007	0.6	0.001–0.005
Prevalent: R^2 = 0.48			
Systolic BP	<0.0001	0.49	0.15–0.4
FGF-23	0.002	0.38	0–0.002
Age	0.012	0.3	0.084–0.63

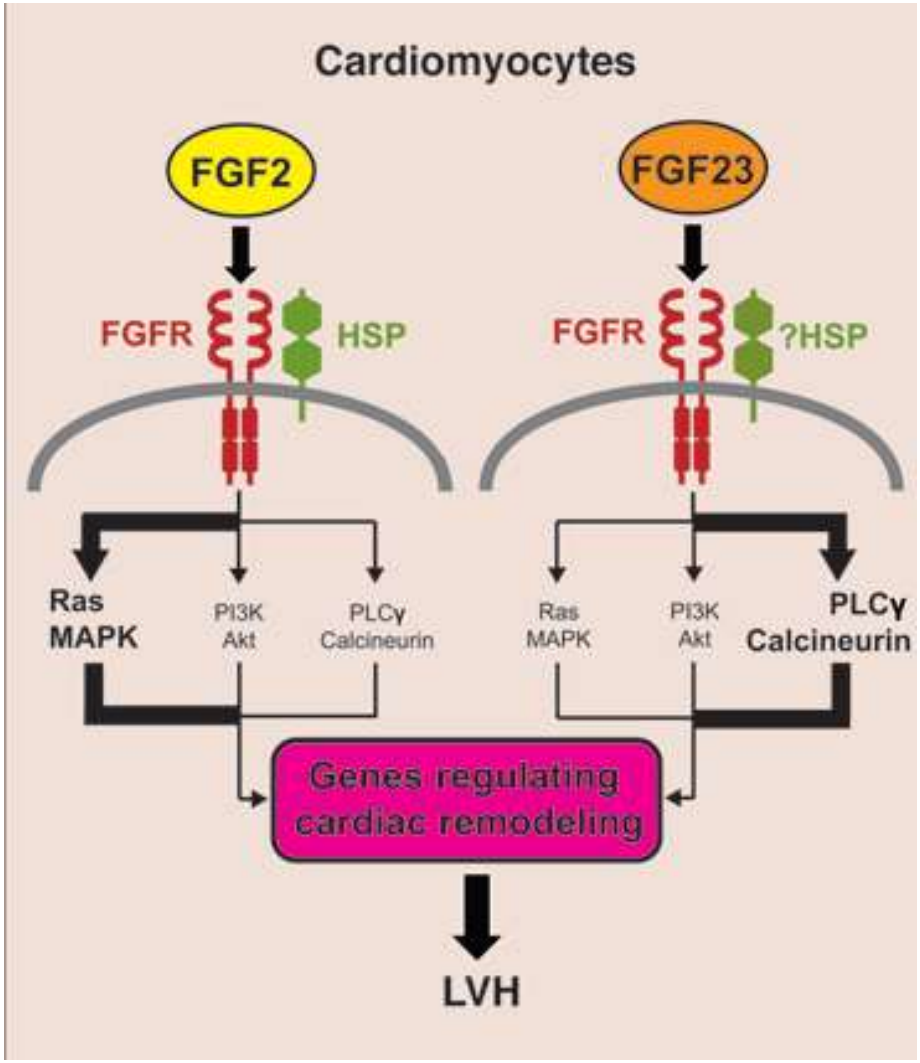
NasrAllah et al, NDT,2010

- ?hyperphosphatemia
- ?hyperparathyroidism
- ?calcitriol intake
- ?decreased clearance
- ?other mechanisms



Razzaque, 2009, NDT

FGF-23 stimulates tyrosine kinases



Faul et al, 2011

FGF23 neutralization improves chronic kidney disease–associated hyperparathyroidism yet increases mortality

Victoria Shalhoub,[1] Edward M. Shatzen,[1] Sabrina C. Ward,[1] James Davis,[1] Jennitte Stevens,[2] Vivian Bi,[2] Lisa Renshaw,[2] Nessa Hawkins,[2] Wei Wang,[2] Ching Chen,[2] Mei-Mei Tsai,[2] Russell C. Cattley,[3] Thomas J. Wronski,[4] Xuechen Xia,[4] Xiaodong Li,[1] Charles Henley,[1] Michael Eschenberg,[5] and William G. Richards[1]

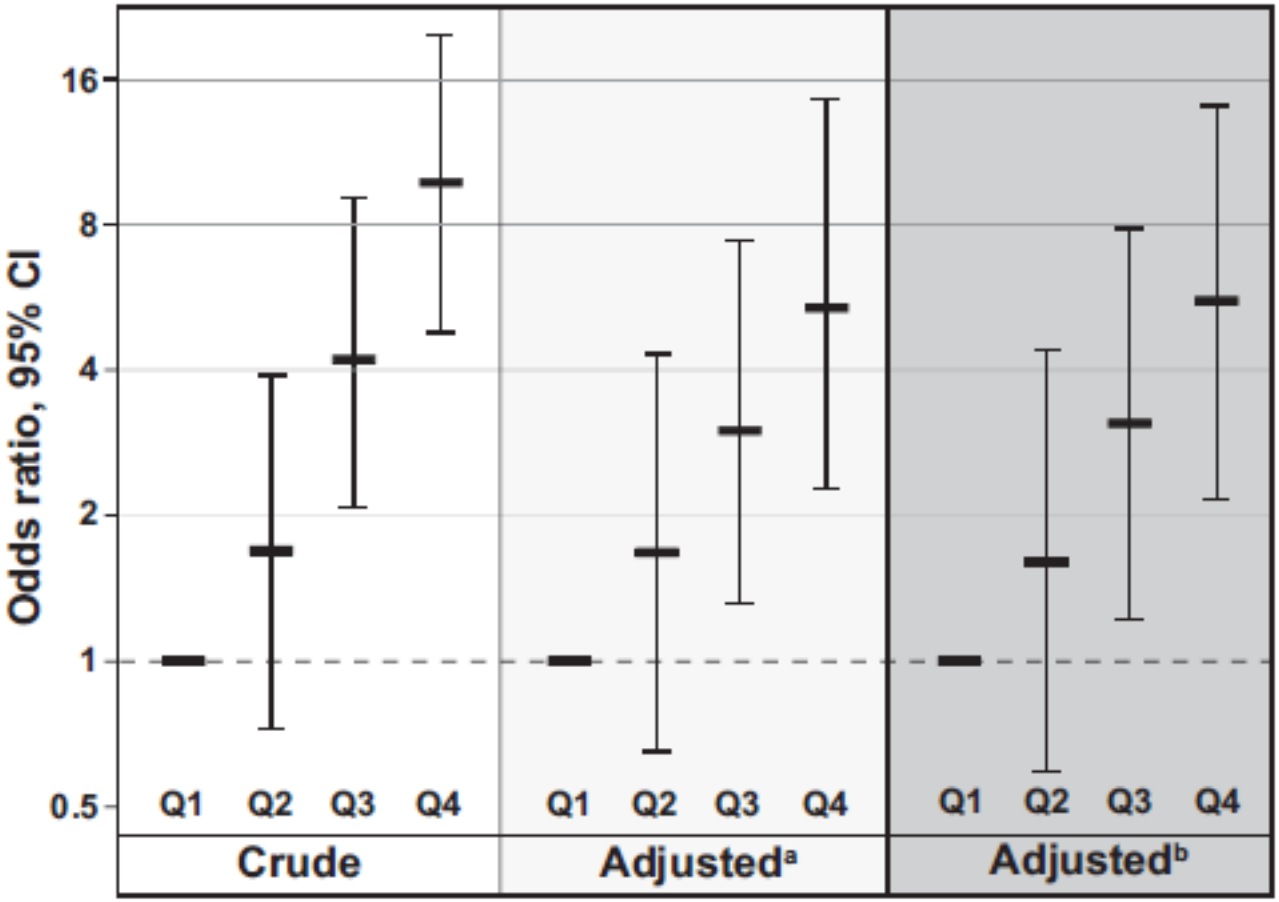
Fibroblast growth factor 23 is not associated with and does not induce arterial calcification

Julia J. Scialla[1,12], Wei Ling Lau[2,12], Muredach P. Reilly[3], Tamara Isakova[1], Hsueh-Ying Yang[4], Matthew H. Crouthamel[4], Nicholas W. Chavkin[4], Mahboob Rahman[5], Patricia Wahl[1], Ansel P. Amaral[1], Takayuki Hamano[6], Stephen R. Master[7], Lisa Nessel[6], Boyang Chai[6], Dawei Xie[6], Radhakrishna R. Kallem[3], Jing Chen[8], James P. Lash[9], John W. Kusek[10], Matthew J. Budoff[11], Cecilia M. Giachelli[4] and Myles Wolf[1] for the Chronic Renal Insufficiency Cohort Study Investigators

Scialla JJ, KI, 2012

SO, WHAT IS GOING ON??

Association of ascending quartiles of FGF-23 with severe inflammation



Mendoza, CJASN, 2012

- FGF-23 is clearly associated with vascular calcification but possibly not through a direct causative effect
- FGF-23 is associated with inflammation
- Inflammation is associated with vascular calcification (and is possibly directly causative, including AGE's)

EXTRA nephron Journals

Original Paper

The Association between Fibroblast Growth Factor-23 and Vascular Calcification Is Mitigated by Inflammation Markers

Mohamed M. NasrAllah[a] Amal R. El-Shehaby[b] Noha A. Osman[a]
Tarek Fayad[a] Amr Nassef[c] Mona M. Salem[d] Usama A.A. Sharaf El Din[a]

Stepwise multiple regression analysis of factors correlating to FGF-23, $R^2$0.68

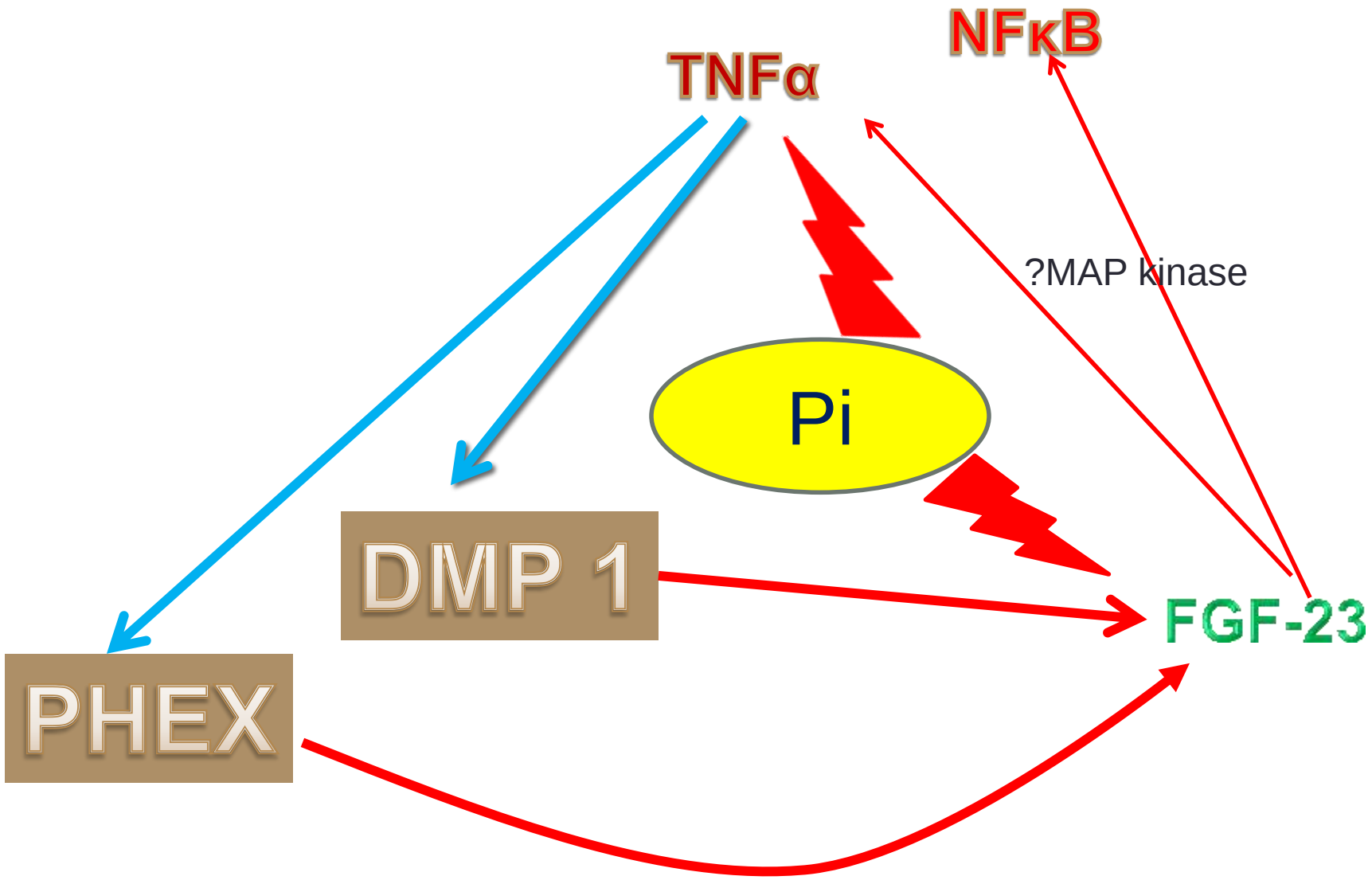
	Beta	P	95% CI
hsCRP	**0.6**	**<0.0001**	**387-634**
AOPP	**0.4**	**<0.0001**	**8-20**
Phosphorus	**0.3**	**<0.0001**	**273-733**

NasrAllah et al, Nephron Extra, 2013

	Beta	P	95% CI
hsCRP	0.47	<0.0001	0.7-1.7
SBP	0.33	<0.0001	0.1-0.3
esRAGE	-0.3	0.001	-0.06- -0.014
Vintage	0.16	0.04	0.06- 0.1

Stepwise multiple regression analysis of factors correlating to ACI, $R^2$0.65

NasrAllah et al, Nephron Extra, 2013


NFκB
TNFα
?MAP kinase
Pi
DMP 1
FGF-23
PHEX


DR. JEKYLL
and MR. HYDE
A ROUBEN MAMOULIAN
Production
FREDRIC MARCH
MIRIAM HOPKINS and ROSE HOBART